# Reviewing the Scientific Symposium "*Estetrol (E4), a landmark in the making? Before and beyond reproductive age: new therapeutic opportunities for E4*" at the 20th World Congress ISGE (11-14 May 2022)

From May 11 till May 14, 2022, the International Society of Gynecological Endocrinology (ISGE) organized the 20th World Congress in Florence, Italy for the first time since the beginning of the Covid-19 pandemic. This congress, which took place in a hybrid format, supported the medical and scientific community in sharing new data, knowledge and insights into scientific developments and innovations in the field of gynecological endocrinology.

In a session on the first day, five key experts presented a holistic view. Some of them broadened the horizon of Estetrol (E4) before and beyond reproductive age by discussing its opportunities and safety profile in a variety of therapeutic areas in addition to contraception, including menopause, Covid-19 and perinatal brain damage.

**Professor Jean-Michel Foidart** (University of Liège, Belgium) opened the scientific symposium by introducing E4, a native, naturally-occurring estrogen produced by the human fetal liver, and briefly explained its unique mode of action. Like all other estrogens, E4 can bind and activate the nuclear estrogen receptor alpha (ERα), which upon binding of E4, dimerizes and recruits specific co-regulators and co-inhibitors that are identical to those recruited by estradiol (E2) or estriol (E3), while selective estrogen receptor modulators (SERMs) recruit others. However, unlike other estrogens, E4 can block the membrane-initiated steroid signaling in several tissues, including the breast, and can antagonize this pathway in the presence of E2 (Abot 2014, Arnal 2017, Foidart 2019, Gérard 2022). With this unique mode of action, Professor Foidart showed that E4 is the first Native Estrogen with Selective Tissue-activity (NEST), and for the first time, a new combined oral contraceptive pill containing E4 as its estrogenic component (E4 15 mg as monohydrate/drospirenone [DRSP] 3 mg) was recently approved in Canada, United States, Europe and Australia.

## Addressing menopausal women's needs with E4

**Professor Amanda Black** (Ottawa Hospital, Canada) continued her presentation by providing insights into the clinical potential of E4 to address menopausal women's health needs and the opportunities of E4 for oral treatment of menopausal symptoms. A multicenter, randomized, dose-finding, double-blind, placebo-controlled study in postmenopausal women showed significant reduction in weekly vasomotor symptoms (VMS) frequency with E4 15 mg compared to placebo, both at 4 and 12 weeks of treatment. Similarly, the decrease in the severity of VMS was significantly more pronounced after E4 15 mg compared to placebo, both at 4 and 12 weeks of treatment (Gaspard et al. 2020). Secondary endpoints included the impact on genitourinary symptoms; vaginal dryness improved significantly in the E4 15 mg group as did vaginal pain associated with sexual activity in the E4 5, 10 and 15 mg groups. Health-related quality of life improved for all treatment groups, with the highest reduction with E4 15 mg treatment, particularly for somato-vegetative symptoms (Gaspard et al. *in preparation*).

These primary efficacy outcomes were corroborated by two recent, multicenter, double-blind, placebo-controlled phase 3 trials in postmenopausal women that measured the treatment effects of VMS frequency and severity at E4 15 and 20 mg. Results demonstrated a meaningful reduction in VMS frequency and severity *versus* baseline (decrease of 80% and 56%, respectively) and compared to placebo. Secondary endpoints evaluated at 3 months suggested a positive effect of E4 on quality of life including VMS, mood swings, anxiety, sleep, joint pain, libido, skin and hair quality.

## Safety profile of E4: recent clinical evidence

**Professor Jonathan Douxfils** (University of Namur and QUALIblood, Belgium) further elaborated on the favorable safety profile of E4 and provided a brief overview of the coagulation cascade and the risk of venous thromboembolism (VTE), a rare but serious adverse event that is associated with the use of hormonal therapy (HT), which is linked to acquired resistance towards activated protein C (APCr). Using results from a multicenter, randomized, double-blinded study in postmenopausal women, Professor Douxfils demonstrated that E4 15 mg did not impact levels of triglycerides, total cholesterol and LDL-C after 12 weeks of treatment. HDL-C was shown to be significantly increased while the ratio of total cholesterol on HDL-C as well as the level of HbA1c was significantly reduced, showing a favorable profile of E4 on lipid and glycemic functions.

In addition, compared to placebo, E4 15 mg showed no differences in hemostasis parameters, except for slight increases in APCr and sex hormone binding globulin (Douxfils et al., *in preparation*). In line, in women of contraceptive age, the results from a randomized, single-center, open-label, comparative study showed that E4 15 mg in combination with DRSP 3 mg had a favorable impact on lipid function and significantly lower impact on several hemostasis parameters, including APCr, compared to ethinylestradiol (EE) combined with DRSP or levonorgestrel (Douxfils et al. 2020; Klipping et al. 2021). Thus, E4, either alone or in combination with DRSP, was shown to have a favorable lipid and glycemic profile while its impact on hemostasis was negligible, thereby elucidating that the choice of estrogens can modulate its impact on hemostasis function. Data from large phase 3 contraceptive trials enrolling 3,425 premenopausal women further suggested that the use of E4/DRSP is associated with low adverse events rates and risk of VTE (Creinin et al. 2021; Gemzell Danielsson et al. 2022).

These findings are in line with a recent model that has been developed to predict the risk of VTE in users of combined oral contraceptives (Morimont et al. 2020). Although prospective data are needed to confirm these results, it was shown that E4 15 mg, when administered to high-risk female and male patients hospitalized with moderate COVID-19, had no safety concerns. Given the fact that patients, all of whom received standard-of-care heparin, had similar rates of COVID-19-related clotting events in the E4 15 mg and placebo treatment groups (Utian 2021, NAMS), these data further strengthen the safety profile of E4.

## Exploring new frontiers with estrogens: recent developments with E4 for protection in perinatal brain damage

**Professor Pierre Gressens** (INSERM, Paris, France) shed light on perinatal brain injury and the role of neuroinflammation and discussed recent developments with E4 for the protection of perinatal brain damage. Estrogens are known to play an important role in the development and function of the central nervous system (CNS), and the neuroprotective effect of estrogens, including E2 and E4 has been demonstrated in various *in vitro* and *in vivo* models of CNS disease.

Given the fact that fetal plasma levels of E4 are 12 times higher than maternal levels, E4 may play an important role during fetal development. Using different preclinical models of neonatal and adult brain injury, E4 showed various beneficial effects within the pathophysiologic cascade of hypoxic-ischemic encephalopathy, including a reduction of excitotoxic glutamate and gamma-aminobutyric acid release, calcium and nitrate brain levels, oxidative stress, neuronal necrosis and apoptosis, and neuro-inflammation. Furthermore, it has been shown that E4 has the potential to trigger mechanisms of brain repair including neurogenesis, angiogenesis and myelination (Tskitishvili et al. 2014, 2016, 2017 and 2019; Viellevoye et al. *in preparation*).

## "New therapeutic opportunities for estrogens: optimizing cognition and brain health at midlife and beyond"

Finally, **Professor Pauline Maki** (University of Illinois, Chicago, USA) looked into new opportunities for estrogens and discussed the impact of the menopausal transition on cognition and brain health at midlife and beyond, the factors that can lead to cognitive difficulties and the effects of hormone therapy on memory complaints, which are common during and after the menopausal transition, affecting 39% of healthy women aged 40–55 years (Gold et al. 2000).

Professor Maki presented data from large prospective studies, which provided reliable evidence that women experience declines in objective memory performance across the menopause transition and explained that a clear understanding of the factors that contribute to cognitive difficulties in the menopause transition is key to identifying effective treatments for those difficulties. One general mechanism by which menopause may impact memory is through direct effects of estrogen withdrawal on brain systems such as the hippocampus and prefrontal cortex that are rich in estrogen receptors. Neuroimaging studies showed enhanced function in these areas during hormone therapy, and basic science studies demonstrated enhanced hippocampal neurogenesis and other neuroprotective effects of estrogens, including E4 (Tskitishvili et al. 2014 and 2016). VMS and VMS-related sleep difficulties may also contribute to memory dysfunction and recent data suggested that VMS, only when objectively measured with ambulatory monitors but not when self-reported, were associated with memory declines and adverse effects on brain health, including hippocampal dysfunction, ischemic damage, elevated cortisol and sleep disruption (Maki et al. 2020).

Initial clinical trial data suggested that effective VMS treatments may improve memory (Maki et al. 2016). Hence, estrogenic treatments may benefit memory through direct effects on estrogen receptors in memory circuits as well as through indirect improvements in VMS.

Furthermore, Professor Maki explained that randomized trials generally showed that hormone therapy has neutral effects on cognition in early postmenopausal women and beneficial effects on cognition after oophorectomy and that trials including women aged 65 and older showed cognitive risk of certain forms of hormone therapy (conjugated equine estrogen/medroxyprogesterone acetate; CEE/MPA) but not others (oral E2). Data from the Women's Health Initiative indicated that estrogen therapy, when given after the age of 65, is associated with a decreased odds of death from Alzheimer's disease. Unfortunately, there are no clinical trial data informing our understanding of any form of estrogen on cognition in women with bothersome VMS.

## Concluding Remarks

### Estetrol (E4), a landmark in the making? Before and beyond reproductive age: new therapeutic opportunities for E4

- E4 clinical trials demonstrated a significant reduction in VMS severity and frequency, improved quality of life, and reduction of symptoms of GSM
- E4 alone, or in association with DRSP, demonstrated a favorable lipid, glycemic and hemostasis profile
- E4 shows neuroprotection in a preclinical model of perinatal brain damage

### New therapeutic opportunities for estrogens: optimizing cognition and brain health at midlife and beyond

- Memory performance declines in the perimenopause due to a decrease in estrogen levels and increased VMS frequency
- The impact of VMS on cognitive function deserves more attention